Meat, fish, and ovarian cancer risk: results from 2 Australian case-control studies, a systematic review, and meta-analysis[1–3]

Fariba Kolahdooz, Jolieke C van der Pols, Christopher J Bain, Geoffrey C Marks, Maria Celia Hughes, David C Whiteman, and Penelope M Webb for the Australian Cancer Study (Ovarian Cancer) and the Australian Ovarian Cancer Study Group

ABSTRACT

Background: Variation in meat and fish intakes has been associated with a risk of some cancers, but evidence for ovarian cancer is limited and inconsistent.

Objective: We examined the association between intakes of total meat, red meat, processed meat, poultry, and fish and ovarian cancer risk.

Design: Data came from 2 Australian population-based case-control studies conducted 10 y apart. Analyses included a total of 2049 cases and 2191 control subjects. We obtained dietary information via a food-frequency questionnaire. We estimated multivariable-adjusted odds ratios (ORs) for each study by using logistic regression and combined results of the 2 studies by using random-effects models. We also assembled the published evidence in a systematic review and meta-analysis.

Results: Although there was no association between total or red meat intake and ovarian cancer risk, women with the highest intake of processed meat had a significantly increased risk of ovarian cancer in the 2 case-control studies (combined OR: 1.18; 95% CI: 1.15, 1.21) and the meta-analysis [7 studies; pooled relative risk (RR): 1.20; 95% CI: 1.07, 1.34]. In contrast, a frequent intake of poultry was associated with borderline significant reductions in risk in the 2 case-control studies (combined OR: 0.83; 95% CI: 0.67, 1.03) and the meta-analysis including 7 additional studies (pooled RR: 0.90; 95% CI: 0.79, 1.01). High fish intake was associated with a significantly reduced risk in the 2 case-control studies (combined OR: 0.76; 95% CI: 0.62, 0.94) and a smaller borderline significant reduction in the meta-analysis (6 additional studies; pooled RR: 0.84; 95% CI: 0.68, 1.03).

Conclusion: Our results suggest that low consumption of processed meat and higher consumption of poultry and fish may reduce the risk of ovarian cancer. *Am J Clin Nutr* 2010;91:1752–63.

INTRODUCTION

Ovarian cancer is the sixth most common cancer in women worldwide, and mortality is high (1). Identification of potentially modifiable factors contributing to its cause may help reduce the burden of this disease. Although the associations between oral contraceptive use, parity, and family history and ovarian cancer risk are well defined (2, 3), the role of other factors, such as diet, remains controversial. Although dietary risk factors have been reported, the data are sparse and inconsistent, and a recent review (4) concluded that there was limited evidence for a decreased risk with consumption of nonstarchy vegetables.

Previous studies suggested a potential link between a high intake of meat, in particular red meat and processed meat, and the risk of several types of cancer including colorectal, stomach, breast, and prostate cancers (4). Red meat and processed meat are sources of saturated fat and iron, which have independently been linked to carcinogenesis (5, 6). In addition, processed meats contribute to the formation of carcinogenic and mutagenic N-nitroso compounds (7) and heterocyclic amines (8). In contrast, the polyunsaturated omega-3 fatty acids in fatty fish are thought to reduce the risk of some types of cancer (9).

An early ecologic study (10) reported a positive association between per capita meat consumption and ovarian cancer mortality, and in a previous study, Kolahdooz et al (11) observed a >2-fold increased risk of ovarian cancer among women who reported eating a diet high in meat and fat, which suggested a potential link between meat intake and ovarian cancer risk. Positive associations between a high intake of red meat (12, 13) or processed meat (12) and ovarian cancer risk were also reported in hospital-based case-control studies in Italy, although other studies (14, 15) observed no relation. Similarly, although some case-control studies suggested risk reductions ranging from 25% to 75% for frequent compared with infrequent intake of poultry (16, 17) or fish (9, 12, 16), other studies have shown either no association (18–20) or a positive association with fish intake (21–23). However, 2 of the latter 3 studies were from China (22) and Japan (23), and the observed positive associa-

[1] From the Genetics and Population Health Division, Queensland Institute of Medical Research, Brisbane, Queensland, Australia (FK, JCvdP, CJB, MCH, DCW, and PMW); the School of Population Health, The University of Queensland, Brisbane, Queensland, Australia (FK, CJB, and GCM); and the Iran University of Medical Sciences, Tehran, Iran (FK).

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[3] Address correspondence to PM Webb, Gynaecological Cancers Group, Queensland Institute of Medical Research, Post Office Royal Brisbane Hospital, Queensland 4029, Australia. E-mail: penny.webb@qimr.edu.au.

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tions might have been due to consumption of preserved or salted fish. Cohort studies unanimously reported null results for the association between the intake of red meat (14, 24), poultry (24–26), or fish (14, 24, 26) and ovarian cancer risk, but these studies included <400 cases. Overall, results from case-control studies have been inconsistent.

In this article, we further investigate the relation between the intake of total meat, red meat, processed meat, liver, poultry and fish and ovarian cancer risk by using data from 2 Australian case-control studies. We also brought together all of the published data to comprehensively examine these associations in a systematic review and meta-analysis. Our hypothesis was that the intake of red and processed meats would be positively associated, and the intake of chicken and fish would be inversely associated, with risk of ovarian cancer.

SUBJECTS AND METHODS

Data were obtained from 2 separate Australian studies of epithelial ovarian cancer conducted 10 y apart. Both studies were approved by human research ethics committees, and all women provided informed consent.

Survey of Women's Health

Details of the Survey of Women's Health (SWH) study were described previously (11). Briefly, the study included a total of 793 women who were newly diagnosed with epithelial ovarian cancer between the ages of 18 and 79 y in the Australian states of New South Wales, Victoria, and Queensland between 1990 and 1993 (response rate: 90%). Control subjects, matched to cases by state of residence and 5-y age group, were selected at random from the electoral roll (enrollment to vote is compulsory in Australia). Of 1173 eligible women, 855 (73%) participated. For the current analyses, we excluded 125 women who did not return a food-frequency questionnaire (FFQ), 47 women with >10% of items missing on the FFQ, and 16 women whose estimated energy intake was very extreme (<500 or >3500 kcal) (27), which left a final group of 683 cases and 777 control subjects for analyses.

Australian Ovarian Cancer Study

Details of the Australian Ovarian Cancer Study (AOCS) were reported previously (28). Cases were women aged 18–79 y who were newly diagnosed with invasive or borderline epithelial ovarian, fallopian tube, or primary peritoneal cancer between 2002 and 2005. Of the 3550 women identified as potentially eligible for the study, 805 (18%) women were excluded for the following reasons: death (n = 307), their doctor did not give permission for them to be contacted (n = 133), they could not be contacted (n = 194), language difficulties (n = 70), mental incapacity (n = 35), or illness (n = 66). The remaining 2745 women with a clinically suspected diagnosis of ovarian cancer were invited to participate, and of these, 2319 (85% of those approached and 65% of those originally identified) women agreed to take part in the study. After surgery, an additional 590 women were excluded when a pathology review showed that they did not have an eligible cancer, 19 women were excluded because their cancer was first diagnosed before the study period, and one woman was excluded because she was not an Australian resident at the time of her initial diagnosis. Of the final 1709 cases, 1612 (94%) women returned the main study questionnaire. Control subjects were selected randomly from the Australian Electoral Roll between 2002 and 2005 by using the same procedures used for the SWH. Of the 3442 eligible women contacted, 1615 (47%) of them consented to participate. Six women with a history of ovarian cancer, 99 women who reported a previous bilateral oophorectomy, and one woman who did not complete the main study questionnaire were excluded, leaving 1509 women in the control group. For the current analyses, we excluded 157 cases and 48 control subjects who did not return the FFQ, 26 cases and 3 control subjects with >10% of FFQ items missing, and 63 cases and 44 control subjects whose estimated energy intake was very extreme (<700 or >4000 kcal; these cutoffs were increased from those used in the SWH to reflect the general increase in dietary intake over the 10 y between the 2 studies), leaving a final group of 1366 cases and 1414 control subjects for analyses.

Women in both studies provided detailed health and lifestyle information via a standardized face-to-face interview in the SWH or a self-administered questionnaire in the AOCS. Information on dietary intake was collected by using very similar self-administered FFQs on the basis of the instrument originally developed and validated in the United States by Willett et al (29) but adapted for and validated in the Australian setting (30–32). The FFQ asked respondents to recall how often, on average, they consumed a standard serving size of foods in the previous year (for cases before their cancer was diagnosed); frequency responses ranged from never to ≥4 times/d.

The average frequency of consumption of each food group was estimated by summing the frequency of intake of the individual foods that made up that group; totals were categorized into 3 or 4 groups for further analyses. Total meat intake included consumption of beef, lamb, or pork as a main or mixed dish (also classified as red meat); chicken with and without skin; and processed meats. Total fish intake included consumption of canned tuna and dark-meat fish such as sardines (also classified as fatty fish), other types of fish (also classified as nonfatty fish), fish sticks, and seafood such as prawns and crabs.

Cutoffs for categories were defined separately for each food group to allow the same cutoffs on the basis of whole numbers of servings to be used for both studies while maintaining sufficient numbers in each group for analyses. Tests for trends were performed over categories of food intake, modeling the median values of each category as a single continuous variable. Analysis of variance was used to test for differences in means for continuous variables, and the chi-square test was used for categoric variables. Unconditional multiple logistic-regression models were used to estimate the relative risk (RR) of cancer associated with each food group, adjusted for potential confounders including age (in years and age-squared), parity, oral contraceptive use, level of education, and energy intake (log transformed). Other potential confounders that were not included in the final models because they did not substantially alter risk estimates were as follows: menopausal status, family history of breast or ovarian cancer in a first-degree relative, use of hormone replacement therapy, tubal ligation, hysterectomy, talc use, smoking, alcohol consumption, and body mass index. Results are presented as odds ratios (ORs) and 95% CIs compared with the lowest intake categories. The 2 data sets were initially analyzed

separately and then combined by calculating weighted, pooled risk estimates by using random-effects models. To test for the linear trend in combined models, the estimates of effect for continuous versions of the explanatory variables were combined, and a *Z* statistic was calculated from the coefficient and SE of the combined OR. The presence of heterogeneity between the 2 studies was tested by using Cochran's Q test. All tests were 2-sided, and $P < 0.05$ was considered statistically significant.

Systematic review and meta-analysis

The systematic review was conducted according to the Meta-analysis Of Observational Studies in Epidemiology guidelines for reviews of observational studies (33). We included observational studies of all designs that presented risk estimates for the association between incident ovarian cancer and consumption of total meat, red meat (including fresh meat, beef, pork, or lamb), processed meat (including sausages), chicken or poultry, fish or shellfish, or liver. Eligible studies were identified by 2 authors (FK and PMW) who searched the MEDLINE database (1950–November 2009; US National Library of Medicine, Bethesda, MD) with OvidSP software (Ovid Technologies, Wolters Kluwer, New York, NY) as the interface and EMBASE (1966–November 2009; Elsevier Science, Amsterdam, Netherlands) with the EMBASE search interface and the Science Citation Index (1990–November 2009; Thomson Reuters, New York, NY). Searches used the following MeSH terms or text words: "ovarian neoplasms" or "ovar$" and "cancer" or "neoplasm"; and "diet," "meat," "poultry," "chicken," or "liver" or "fish" combined with "diet." The search was confined to full articles published in English through November 2009. Additional studies were identified by searching the reference lists of identified articles and the Science Citation Index for eligible articles that were commonly cited to identify subsequent studies that had cited them. We read the abstracts of all identified studies to exclude those that were clearly not relevant. The full texts of the remaining articles were read to determine whether they met the inclusion criteria.

The following information was extracted for the relevant studies: country, year of publication, study type, numbers of cases and controls/cohort size, response/follow-up rates, years of and age at diagnosis, cancer types included, dietary questionnaire used, food items studied, and intakes compared, confounders considered, and risk estimates for comparisons of the highest with the lowest category of intakes. The extracted data were checked independently by 2 authors (FK and PMW).

For the meta-analysis, we assumed that estimates of ORs from case-control studies and risk or rate ratios from cohort studies were all valid estimates of the RR (34). To pool RR estimates, we calculated a weighted average of the log RR, taking into account the random effects by using the method of DerSimonian and Laird (35). We assessed heterogeneity for each pooled estimate by using Cochran's *Q* test and publication bias by using Begg's rank correlation test and Egger's regression method (36). As recommended in the Meta-analysis Of Observational Studies in Epidemiology guidelines (33), we also conducted analyses stratified by key features of study design to assess the effects of varying study quality on our results. All analyses were conducted with the SAS statistical package (version 9; SAS Institute Inc, Cary, NC) and Stata 10 (StataCorp LP, College Station, TX).

RESULTS

Characteristics of the participants in the 2 studies are shown in **Table 1**. In the AOCS, the mean age of cases was slightly higher than that of control subjects. SWH cases were slightly less likely than control subjects to have continued their education after leaving high school. In both studies, cases were less likely than control subjects to have had a pregnancy, used the oral contraceptive pill for >5 y, or had a tubal ligation, but cases were more likely to have used talc in the perineal region or to have a first-degree relative with breast or ovarian cancer.

The risks of ovarian cancer associated with meat and fish intake are shown in **Table 2**. In the analyses combining the 2 studies, there was no evidence of heterogeneity for any of the meat/fish groups. Consumption of total meat and red meat was not associated with ovarian cancer risk in either study population or in the combined analysis. Compared with women in the lowest group of processed meat intake, women in the highest group had a significantly increased risk of ovarian cancer (combined multivariable adjusted OR for the highest group compared with the lowest group: 1.18; 95% CI: 1.15, 1.21; *P* for trend = 0.03). Additional adjustment for intake of fruit, vegetables, and dairy products did not substantially change the observed associations for meat, red meat, or processed meat, but after adjustment for fat intake, the association with processed meat was weakened slightly and was only borderline significant (combined OR for the highest group compared with the lowest group: 1.18; 95% CI: 0.95, 1.46; *P* for trend = 0.09). Liver intake was also significantly positively associated with the risk of ovarian cancer in both studies giving a combined multivariable adjusted OR for women who reported consuming more than one serving of liver per month compared with those who reported never consuming liver of 1.48 (95% CI: 1.20, 1.81; *P* for trend = 0.002). Further adjustment for fat intake did not alter the direction or strength of this association, but adjustment for retinol (liver is a rich source of dietary retinol) almost completely attenuated the OR (combined OR: 1.08; 95% CI: 0.94, 1.23).

There was a suggestion of a reduced risk of ovarian cancer associated with high poultry intake with a nonsignificant 15–20% reduction in the risk of ovarian cancer for women who reported consuming >3 servings of poultry/wk compared with those who ate <1 serving of poultry/wk, but the trend of decreasing risk with increasing intake reached statistical significance only in the SWH ($P = 0.002$). There was also an inverse association between consumption of total fish and fatty fish and risk, although this was significant only in the AOCS and the combined analyses (combined OR for ≥4 servings of all fish/wk compared with <1 serving of all fish/wk: 0.76; 95% CI: 0.62, 0.94; *P* for trend = 0.008; ≥6 servings of fatty fish/wk compared with <1 serving of fatty fish/wk: 0.79; 95% CI: 0.65, 0.98; *P* for trend = 0.03). We also observed a nonsignificant reduction in risk associated with the highest amount of consumption of nonfatty fish in the SWH but not in the AOCS. Combining the 2 studies suggested a borderline significant reduction in risk among women eating ≥4 servings of nonfatty fish/mo, although the trend with increasing consumption was not significant. Additional adjustments for intakes of fruit, vegetables, dairy products, and

TABLE 1
Comparison of nondietary and lifestyle characteristics of 683 cases and 777 control subjects in the Survey of Women's Health (SWH; 1990–1993) and 1366 cases and 1414 control subjects in the Australian Ovarian Cancer Study (AOCS; 2002–2005), Australia

	SWH			AOCS		
Variable	Cases	Control subjects	P^1	Cases	Control subjects	P^1
Age (y)	54.9 ± 13.1[2]	54.6 ± 14.2	0.6	57.6 ± 11.9	56.3 ± 12.5	0.003
Postmenopausal [*n* (%)]	433 (63.4)	504 (64.9)	0.6	978 (71.6)	936 (66.2)	0.002
Education after high school [*n* (%)]	295 (43.5)	377 (48.8)	0.04	644 (47.1)	719 (50.9)	0.05
Parity [*n* (%)]						
0	160 (23.4)	112 (14.4)		267 (19.6)	166 (11.7)	
1–2	285 (41.7)	307 (39.5)		557 (40.9)	608 (43.0)	
≥3	238 (34.8)	358 (46.1)	<0.0001	539 (39.6)	640 (45.3)	<0.0001
Oral contraceptive use [*n* (%)]						
Never	334 (49.1)	275 (35.7)		431 (31.7)	297 (21.1)	
<60 mo	198 (29.1)	218 (28.3)		364 (26.8)	347 (24.6)	
≥60 mo	149 (21.9)	277 (36.0)	<0.0001	563 (41.5)	766 (54.3)	<0.0001
Tubal ligation [*n* (%)]	97 (14.2)	179 (23.0)	<0.0001	316 (23.2)	386 (27.3)	0.01
Ever use of talc in the perineal region [*n* (%)]	321 (47.0)	311 (40.0)	0.007	675 (49.5)	625 (44.3)	0.006
Family history [*n* (%)][3]	82 (12.0)	63 (8.1)	0.01	255 (18.7)	184 (13.0)	<0.0001
Hysterectomy [*n* (%)]	97 (14.2)	164 (21.1)	0.0006	319 (23.4)	275 (19.5)	0.01
Ever use of hormone replacement therapy [*n* (%)]	109 (16.0)	139 (17.9)	0.3	485 (36.0)	500 (35.4)	0.8
BMI [*n* (%)]						
<25 kg/m^2	404 (60.3)	519 (67.5)		560 (42.4)	642 (46.0)	
25–29.9 kg/m^2	166 (24.8)	177 (23.0)		450 (34.0)	429 (30.7)	
≥30 kg/m^2	100 (14.9)	73 (9.5)	0.0006	312 (23.6)	325 (23.3)	0.1
Smoking status [*n* (%)]						
Never	400 (58.6)	489 (62.9)		775 (56.7)	837 (59.2)	
Past smoker	152 (22.3)	170 (21.9)		370 (27.1)	416 (29.5)	
Current smoker	131 (19.2)	118 (15.2)	0.1	221 (16.2)	160 (11.3)	0.0009

[1] Chi-square statistics and chi-square tests for trends (parity, oral contraceptive use, and BMI) were used to compare proportions; ANOVA was used to compare means. All statistical tests were 2-sided.
[2] Mean ± SD (all such values).
[3] Family history of breast or ovarian cancer in a first-degree relative.

fat did not substantially change the observed associations for poultry, but after adjustment for vegetable intake, the inverse association between total fish and risk was weakened slightly and became nonsignificant (combined OR: 0.83; 95% CI: 0.67, 1.03).

Although we did not have sufficient statistical power to detect small differences, none of the reported associations differed appreciably for the different histologic subtypes of ovarian cancer (data not shown).

The literature search identified 142 potentially relevant publications. After screening the titles and abstracts, 93 were excluded because they were not relevant. We retrieved 49 articles for further review, of which 26 studies presented data that evaluated the association between meat/fish and ovarian cancer risk. Four of these studies were excluded because they were secondary reports from a study that was already included (21, 37, 38) or considered only fried meat (39).

Five studies (**Table 3**) were excluded from the main analyses because they had only adjusted for age and/or education with no consideration of other potential confounders (16, 19, 40, 41) or did not present sufficient information to allow the calculation of CIs (20). The characteristics of the remaining 17 studies (6 cohort studies and 3 population-based and 8 hospital-based case-control studies) and the items evaluated are summarized in **Tables 4** and **5** for cohort and case-control studies, respectively. In one cohort study (26), the reference category for the analyses of total meat, red meat, and fish differed substantially from the other studies, and this study was excluded from these meta-analyses. The final analyses included a total of 7 studies for total meat (15, 18, 23, 24, 42–44), 9 for red meat (12–14, 17, 18, 22, 24, 25, 45), 5 studies for processed meat (12, 14, 18, 24, 45), 7 studies for poultry (12, 17, 18, 22, 24–26), 6 studies for fish (9, 12, 14, 18, 22, 24), and one study for liver (46), together with the SWH and AOCS.

The pooled RR of ovarian cancer for the highest group compared with the lowest group of total meat intake was 1.16 (95% CI: 0.96, 1.40) with significant heterogeneity ($P = 0.04$). After stratifying by study type, the pooled RR were similar and null for cohort and population-based case-control studies [RR for cohort and population-based studies combined = 1.01 (95% CI: 0.85, 1.19)], whereas the pooled estimate for hospital-based case-control studies showed a significant 47% increased risk (**Figure 1**A). The results were similar for red meat with a significant positive association seen only among hospital-based case-control studies and not population-based studies (RR for cohort and population-based studies combined = 1.06; 95% CI: 0.94, 1.21) (Figure 1B). The intake of red meat as a main dish was included in the meta-analysis in preference to meat as a mixed dish for one cohort study (25) that only reported these separately. When we included the estimate for red meat as a mixed dish instead, the estimates were essentially unchanged.

Combining the results of the SWH and AOCS data with the 5 previous studies that evaluated processed meat (12, 14, 18, 24,

TABLE 2
Odds ratios (ORs; with 95% CIs) for the association between intakes of total meat, red meat, processed meat, liver, poultry, fish, and sea foods and ovarian cancer risk in 683 cases and 777 control subjects in the Survey of Women's Health (SWH; 1990–1993) and 1366 cases and 1414 control subjects in the Australian Ovarian Cancer Study (AOCS; 2002–2005), Australia, and combined analyses

	SWH		AOCS		
Food intake	Control subjects/cases	OR (95% CI)[1]	Control subjects/cases	OR (95% CI)[1]	Combined OR (95% CI)[2]
	n		*n*		
Total meat					
<6 servings/wk	218/176	1.0	343/347	1.0	1.0
6–8.9 servings/wk	223/210	1.09 (0.81, 1.45)	426/390	1.01 (0.82, 1.24)	1.04 (0.88, 1.23)
9–11.9 servings/wk	189/164	1.00 (0.72, 1.38)	333/319	1.07 (0.85, 1.34)	1.05 (0.87, 1.26)
≥12 servings/wk	147/133	1.02 (0.72, 1.46)	312/310	1.08 (0.85, 1.39)	1.06 (0.87, 1.30)
P for trend[3]	—	0.9	—	0.5	0.6
Red meat					
<3 servings/wk	210/190	1.0	404/386	1.0	1.0
3–4.9 servings/wk	217/176	0.89 (0.66, 1.20)	397/380	1.05 (0.86, 1.29)	1.00 (0.87, 1.16)
5–6.9 servings/wk	163/156	1.01 (0.73, 1.38)	348/310	1.02 (0.82, 1.27)	1.02 (0.85, 1.22)
≥7 servings/wk	187/161	0.90 (0.65, 1.25)	265/290	1.21 (0.95, 1.53)	1.07 (0.80, 1.42)
P for trend[3]	—	0.7	—	0.2	0.5
Processed meat					
<1 servings/wk	293/203	1.0	499/468	1.0	1.0
1–1.9 servings/wk	240/230	1.42 (1.08, 1.87)	464/432	1.02 (0.85, 1.23)	1.19 (0.86, 1.64)
2–3.9 servings/wk	133/140	1.56 (1.13, 2.16)	266/269	1.17 (0.94, 1.47)	1.32 (1.00, 1.74)
≥4 servings/wk	111/110	1.34 (0.94, 1.91)	185/197	1.18 (0.92, 1.52)	1.18 (1.15, 1.21)
P for trend[3]	—	0.1	—	0.1	0.03
Liver					
Never	483/384	1.0	1014/944	1.0	1.0
<1 serving/mo	215/188	1.09 (0.85, 1.40)	311/295	1.00 (0.83, 1.20)	1.00 (0.97, 1.04)
≥1 serving/mo	76/100	1.67 (1.18, 2.36)	88/117	1.35 (1.00, 1.83)	1.48 (1.20, 1.81)
P for trend[3]	—	0.004	—	0.07	0.002
Poultry					
<1 serving/wk	166/156	1.0	191/209	1.0	1.0
1–1.9 servings/wk	370/359	0.99 (0.75, 1.31)	520/518	1.01 (0.79, 1.28)	1.00 (0.83, 1.20)
2–2.9 servings/wk	147/87	0.57 (0.39, 0.81)	278/292	1.03 (0.79, 1.34)	0.84 (0.68, 1.04)
≥3 servings/wk	94/79	0.79 (0.53, 1.18)	425/346	0.84 (0.65, 1.09)	0.83 (0.67, 1.03)
P for trend[3]	—	0.002	—	0.2	0.1
Total fish					
<1 serving/wk	253/224	1.0	280/286	1.0	1.0
1–1.9 servings/wk	289/224	0.88 (0.68, 1.14)	365/379	0.95 (0.76, 1.19)	0.92 (0.78, 1.09)
2–3.9 servings/wk	122/125	0.95 (0.69, 1.32)	441/412	0.86 (0.69, 1.07)	0.89 (0.74, 1.06)
≥4 servings/wk	85/68	0.77 (0.52, 1.15)	328/289	0.76 (0.60, 0.97)	0.76 (0.62, 0.94)
P for trend[3]	—	0.3	—	0.01	0.008
Fatty fish[4]					
<1 serving/mo	305/268	1.0	277/304	1.0	1.0
1–3.9 servings/mo	271/231	1.00 (0.77, 1.28)	354/364	0.93 (0.74, 1.17)	0.94 (0.89, 1.00)
4–5.9 servings/mo	131/122	1.07 (0.78, 1.46)	412/368	0.80 (0.64, 1.01)	0.90 (0.68, 1.20)
≥ 6 servings/mo	70/62	0.89 (0.60, 1.34)	371/330	0.77 (0.61, 0.97)	0.79 (0.65, 0.98)
P for trend[3]	—	0.7	—	0.03	0.03
Nonfatty fish					
<1 serving/mo	220/196	1.0	319/312	1.0	1.0
1–2.9 serving/mo	207/197	0.98 (0.74, 1.31)	317/312	0.97 (0.77, 1.22)	0.97 (0.81, 1.17)
3–3.9 serving/mo	259/218	0.84 (0.64, 1.12)	459/436	0.94 (0.76, 1.16)	0.92 (0.85, 1.00)
≥4 serving/mo	88/71	0.76 (0.51, 1.12)	319/306	0.90 (0.71, 1.13)	0.86 (0.70, 1.05)
P for trend[3]	—	0.1	—	0.4	0.1
Other seafood[5]					
Never serving/mo	282/264	1.0	406/437	1.0	1.0
<1 serving/mo	310/262	0.94 (0.73, 1.20)	580/525	0.89 (0.74, 1.07)	0.90 (0.78, 1.05)
≥1 serving/mo	184/157	0.89 (0.67, 1.20)	424/392	0.90 (0.73, 1.10)	0.89 (0.75, 1.05)
P for trend[3]	—	0.5	—	0.4	0.4

[1] ORs from logistic regression analysis were adjusted for age (in y), age-squared, oral contraceptive use (never, <60 mo, and ≥60 mo), level of education (school only/further education in the SWH and school only/technical training/university in AOCS), parity (0, 1–2, and ≥3), and energy intake (log transformed).

[2] The 2 data sets were combined by calculating weighted pooled risk estimates with the use of random-effects models.

[3] To test for a linear trend in the combined models, the estimates of effects for continuous versions of the explanatory variables were combined, and a *Z* statistic was calculated from the coefficient and SE of the combined OR.

[4] Fatty fish such as sardines, mackerel, and salmon.

[5] Other seafoods such as prawns, crabs, and scallops.

TABLE 3
Published studies excluded from the meta-analyses of the association between intake of meat/fish and ovarian cancer risk

Country (study)	Cases/control subjects	Years of diagnosis	Food item	Contrast	Values	Reason for exclusion
	n					
Population-based case-control studies						
United States (16)	215/215	1978–1981	Red meat	Weekly compared with <weekly	1.64 (0.53, 5.09)[1]	Unadjusted/adjusted only for age and race (matched)
			Poultry	Weekly compared with <weekly	0.76 (0.38,1.52)[1]	
			Fish	Any compared with never	0.26 (0.10, 0.67)[2]	
China (20)	172/172	1984–1986	Meat	Quartile 4 compared with quartile 1	1.2 [0.30][3]	Adjusted only for age and education; 95% CI not reported
			Red meat	Quartile 4 compared with quartile 1	1.4 [0.19][3]	
			Poultry	Quartile 4 compared with quartile 1	1.1 [0.78][3]	
			Fish	Quartile 4 compared with quartile 1	0.9 [0.70][3]	
Hospital-based case-control studies						
Japan (40)	110/220	1980–1981	Meat	Almost daily compared with less often	1.41 (0.8, 2.5)[2]	Adjusted only for age (matched); includes population in Mori et al (23)
		1985–1986	Fish	Almost daily compared with less often	1.7 (1.0, 2.9)[2]	
India (41)	97/194	1982–1985	Meat	Nonvegetarian compared with vegetarian diet	1.3 (0.7, 2.2)[2]	Adjusted only for age and marital status (matched)
Taiwan (19)	86/369	1993–98	Pork	>1 compared with ≤1 serving/wk	1.40 (0.65, 3.00)[2]	Adjusted only for age, income, and education
			Beef	>1 compared with ≤1 serving/wk	0.81 (0.45, 1.47)[2]	
			Poultry	>1 compared with ≤1 serving/wk	0.77 (0.37, 1.61)[2]	
			Fish	>1 compared with ≤1 serving/wk	0.94 (0.57, 1.56)[2]	

[1] Odds ratio and 95% CI (in parentheses) estimated from raw data provided in the article.
[2] Odds ratio; 95% CI in parentheses; *P* for trend not provided.
[3] Odds ratio; *P* for trend in brackets.

45) gave a significant positive association with an overall summary RR of 1.20 (95% CI: 1.07, 1.34) for the highest intake group compared with the lowest intake group with no significant heterogeneity ($P = 0.88$) (Figure 1C). The results for cohort and case-control studies did not differ appreciably. The one previous study to evaluate liver intake reported an OR of 0.79 (95% CI: 0.54, 1.1); when combined with the SWH and AOCS, a pooled RR of 1.22 (95% CI: 0.80, 1.85) was obtained for the highest intake group compared with the lowest intake group, although there was significant heterogeneity between the studies ($P = 0.009$), which suggested that this estimate may be unreliable (Figure 1D).

For all studies, the pooled RR for the highest group of poultry intake compared with the lowest group of poultry intake was 0.90 (95% CI: 0.79, 1.01) with no significant heterogeneity. When the estimate for chicken with skin was replaced with that for chicken without skin for one cohort study (25) that reported these separately, the overall pooled RR reduced slightly to 0.87 and became significant (95% CI: 0.77, 0.98). Further analyses showed that there was no association between poultry and ovarian cancer risk in the 3 cohort studies combined, but there were nonsignificant 17–19% reductions in risk in the highest intake group among both the population-based and hospital-based case-control studies (Figure 1E). Similarly, the overall pooled analysis for fish suggested a borderline significant reduction in risk in the highest intake group (RR: 0.84; 95% CI: 0.68, 1.03), but the results of the individual studies were quite heterogeneous (P for heterogeneity = 0.003) with no association seen in the 2 cohort studies and nonsignificant 12–25% reductions in risk in the population- and hospital-based case-control studies (Figure 1F).

In addition to the analyses by study type, we conducted additional sensitivity analyses to assess the effects of various study characteristics on our results. Exclusion of the 3 studies (9, 13, 45) that did not include adjustment for parity and/or oral contraceptive use, 2 potentially important confounders for ovarian cancer, or the 7 studies (9, 13, 23, 26, 43, 44, 46) that did not use a full FFQ, and thus could not adjust for energy intake, did not

TABLE 4
Cohort studies included in the meta-analyses of the association between intake of meat/fish and ovarian cancer risk[1]

Country (study)	Cases/cohort	Years of diagnosis	Age at baseline	Diet information	Food items studied	Contrast	RR (95% CI)	*P* for trend
	n		*y*					
United States (42)	139/29,083	1986–1995	55–69	Baseline	Total meats	>17 compared with <9 servings/wk	1.60 (0.89, 2.86)	0.38
United States (25)[2]	301/80,258	1980–1996	30–55	Baseline and 1984, 1986, and 1990	Beef, pork, and lamb (main dish)	≥2 servings/wk compared with 1–3 servings/mo	1.30 (0.93, 1.82)	0.16
					Beef, pork, and lamb (mixed dish)	≥2 servings/wk compared with <1 serving/mo	0.87 (0.58, 1.31)	0.05
					Hamburger	≥1 serving/wk compared with <1 serving/mo	0.86 (0.63, 1.17)	0.07
					Chicken with skin	≥1 serving/wk compared with <1 serving/mo	0.98 (0.73, 1.32)	0.80
					Chicken without skin	≥1 serving/wk compared with <1 serving/mo	0.82 (0.62, 1.07)	0.06
Sweden (14)	288/61,057	1987–2004	40–76	Baseline and 1997	Red meat	≥4 compared with <2 servings/wk	1.01 (0.70, 1.46)	0.27
					Sausage	≥2 servings/wk compared with rare or never	1.37 (0.83, 2.24)	0.24
					Fish	≥3 compared with <1 serving/wk	1.08 (0.75, 1.55)	0.69
United States (26)[3]	71/13,281	1976–1992	≥25	Baseline	Total meat	≥1 serving/wk compared with never	1.69 (0.88, 3.24)	0.06
					Beef	≥1 serving/wk compared with never	1.09 (0.50, 2.38)	0.94
					Poultry	≥1 serving/wk compared with never	1.23 (0.66, 2.32)	0.74
					Fish	≥1 serving/wk compared with never	1.39 (0.73, 2.62)	0.58
United States (45)	149/199,312	1995–2003	50–79	Baseline	Red meat	Quintile 5 compared with quintile 1	1.19 (0.89–1.59)	0.33
					Processed meat	Quintile 5 compared with quintile 1	1.23 (0.92–1.63)	0.30
Europe (24)[4]	581/325,731	1992–2004	21–77	Baseline	Total meat	≥10 compared with <5–6 servings/wk	0.78 (0.52, 1.17)	0.68
					Red meat	≥5 compared with <2 servings/wk	1.04 (0.70, 1.56)	0.89
					Poultry	≥2 compared with <1 serving/wk	1.05 (0.75, 1.47)	0.82
					Processed meat	≥3.5 compared with <1.5 servings/wk	1.25 (0.81, 1.92)	0.23
					Fish	≥3 compared with <1 serving/wk	0.90 (0.56, 1.43)	0.51

[1] RR, relative risk.
[2] Intake of meat as a main dish was included in the meta-analysis in preference to meat as a mixed dish.
[3] Only the result for poultry intake was included in the meta-analysis because the intake categories of total meat, beef, and fish differed substantially from the other studies.
[4] Intakes of meat (80 g/d), chicken (80 g/d), or fish (100 g/d) were converted to an equivalent number of servings per week for consistency.

appreciably affect any of the results (the maximum change in pooled RR was 0.03). Inclusion of the studies excluded a priori because either the reference group was quite different from the other studies (26) or because the studies (16, 19, 40, 41) only adjusted for age and education and/or marital status, and analyses excluding individual studies one at a time also did not modify the estimates substantially for any of the food groups studied.

Results of Begg's and Egger's tests showed no evidence of significant publication bias for any of the foods considered (*P* values for total meat, red meat, and processed meat were ≥0.6; *P* values for poultry and fish were ≥0.2).

DISCUSSION

The null findings for intake of total meat or red meat and ovarian cancer risk in the SWH and AOCS (separately and combined) are in agreement with the results of cohort studies (14, 24, 26, 42) and most other population-based case-control studies (17, 19, 20, 44), as reflected in the null results for these study types in the meta-analysis. It is likely that the positive association between per capita meat consumption and ovarian cancer mortality seen in an ecologic study (10) could be due to confounding, whereas the increased risks seen among hospital-based case-control studies (13, 22, 23, 43) may have resulted from the use of

TABLE 5
Case-control studies included in the meta-analyses of the association between intake of meat/fish and ovarian cancer risk[1]

Country (study)	Cases/control subjects	Years of diagnosis	Age at diagnosis	Food items studied	Contrast	OR (95% CI)	*P* for trend
	n		*y*				
Population-based studies							
United States (46)	327/3129	1991–1994	40–79	Liver	≥0.25 compared with <0.075 servings/wk	0.79 (0.54, 1.1)	0.33
United States (17)[2]	124/696	1986–1991	40–85	Red meat	>6.5 compared with <2 servings/wk	1.22 (0.61, 2.44)	—[3]
				Poultry	>3.5 compared with <1 serving/wk	0.45 (0.22, 0.92)	—[3]
Canada (18)	422/2135	1994–1997	20–76	Total meat	Quartile 4 compared with quartile 1	0.91 (0.67, 1.24)	0.73
				Red meat	Quartile 4 compared with quartile 1	0.78 (0.57, 1.06)	0.10
				Processed meat	Quartile 4 compared with quartile 1	0.98 (0.72, 1.33)	0.82
				Chicken	Quartile 4 compared with quartile 1	0.99 (0.71, 1.37)	0.61
				Fish	Quartile 4 compared with quartile 1	1.16 (0.85, 1.59)	0.50
Hospital-based studies							
Italy (43)[4]	455/1385	1983–1986	<75	Meat	≥7 compared with <4 servings/wk	1.60 (1.21, 2.12)	<0.001
				Ham	≥4 compared with <2 servings/wk	1.55 (1.11, 2.16)	0.03
				Fish	≥2 compared with <1 serving/wk	0.84 (0.61, 1.16)	NS
Japan (23)[5]	56/112	1980–1981 and 1985–1986	≥50	Meat	Almost daily compared with less often	2.7 (1.0, 7.0)	<0.05
				Fish	Almost daily compared with less often	2.54[6]	—[3]
Italy (9)	971/4770	1983–1996	<75	Fish	≥2 compared with <1 serving /wk	0.7 (0.6, 0.9)	<0.05
Italy (13)	971/4770	1983–1996	<75	Red meat	>6 compared with ≤3 servings/wk	1.3 (1.1, 1.6)	≤0.01
Italy (12)	1031/2411	1992–1999	18–79	Red meat	>5.4 compared with <2.2 servings/wk	1.53 (1.13, 2.05)	0.0007
				Processed meat	>2.9 compared with <1.9 servings/wk	1.21 (0.98, 1.49)	0.08
				Poultry	>3.4 compared with <0.9 servings/wk	0.83 (0.57, 1.21)	0.77
				Fish	>2.9 compared with <0.9 servings/wk	0.51 (0.38, 0.70)	0.0002
United States (44)	496/1425	1982–1998	20–87	Meat	>25 compared with ≤9 servings/mo	1.17 (0.80, 1.71)	0.12
Mexico (15)	84/629	1995–1997	20–79	Meat	Tertile 3 compared with tertile 1	1.35 (0.58, 3.14)	0.06
China (22)[2]	254/652	1999–2000	<75	Fresh meat	≥5.5 compared with ≤2 servings/wk	1.98 (1.0, 3.8)	NS
				Poultry	≥2 compared with ≤0.3 servings/wk	0.77 (0.4, 1.4)	NS
				Fish and shellfish	≥ 4 compared with ≤0.7 servings/wk	1.45 (0.80, 2.80)	NS

[1] OR, odds ratio.
[2] Intakes of meat (80 g/d), chicken (80 g/d), or fish (100 g/d) were converted to an equivalent number of servings per week for consistency.
[3] *P* for trend not reported.
[4] The result for ham intake was not included in the meta-analysis because there were no comparable data from other studies; the result for fish was not included because this population was a subset of that reported by Fernandez et al (9).
[5] The result for fish intake was not included in the meta-analysis because the 95% CI was not reported.
[6] 95% CI not reported.

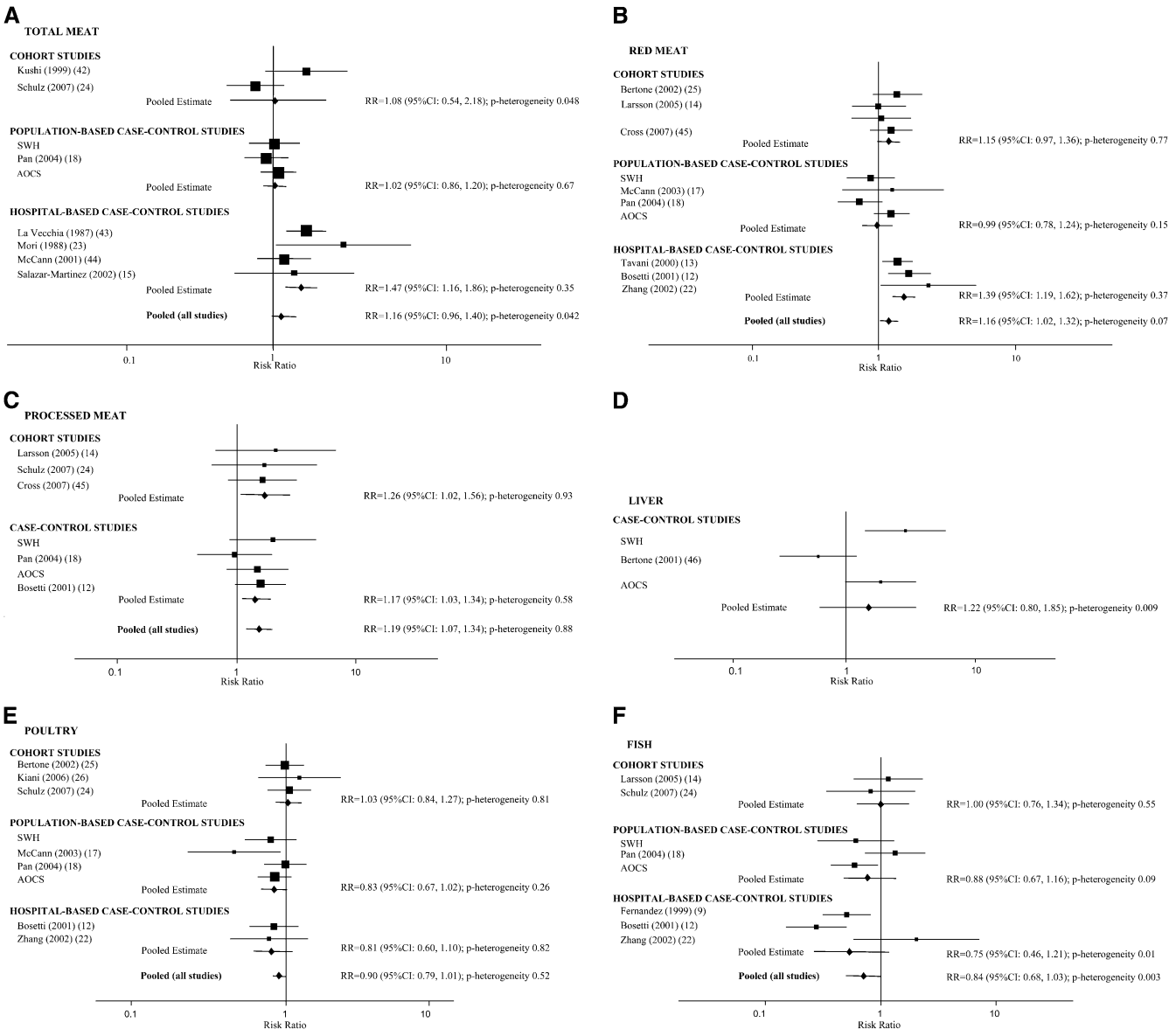

FIGURE 1. Forest plots of the association between intake of total meat (A), red meat (B), processed meat (C), liver (D), poultry (E), and fish (F) and ovarian cancer risk. The center of each square indicates the relative risk (RR) of that study, and the horizontal lines indicate 95% CIs; the area of the square is proportional to the amount of the information from that study; diamonds indicate pooled estimates. RR, relative risk; p-heterogeneity, *P* for heterogeneity; SWH, Survey of Women's Health; AOCS, Australian Ovarian Cancer Study.

hospital control subjects whose dietary intakes may not accurately represent those in the source population (47).

An association between processed meat intake and ovarian cancer has been evaluated less frequently. The positive findings of the SWH and AOCS (individually and combined) are in agreement with those from a large Italian case-control study (12) and 2 cohort studies (14, 24), although a Canadian case-control study showed no association (18). Our meta-analysis combining all of the data provided some evidence of an association between the high intake of processed meat intake and ovarian cancer risk, with significant positive associations seen in our pooled results for both cohort and case-control studies. In previous analyses from the SWH, Kolahdooz et al (11) observed a 2-fold increased risk of ovarian cancer for a dietary pattern high in meat and fat. Both red and processed meat contributed substantially to this dietary pattern, but our current results suggest the association with ovarian cancer may be due less to the high consumption of red meat and more to other components of the meat and fat pattern such as processed meat.

In the SWH and AOCS, there was a strong association between high liver intake and ovarian cancer risk that appeared to be explained by the high concentrations of retinol in liver. The only other study (46) to evaluate the relation between liver and ovarian cancer showed a nonsignificant reduction in risk, although liver intake was considerably lower in the US study (46), and there were few cases (n = 38) in the highest intake category limiting the power to detect an association.

Our findings of a possible decreased risk of ovarian cancer with high consumption of poultry are consistent with the results of previous hospital-based case-control studies (12, 19, 22) and 2

population-based case-control studies (16, 17) but contrast with the results from cohort studies (24–26). Combining all of the data suggested a modest and borderline significant inverse association, although there was considerable heterogeneity between the pooled results from cohort and case-control studies.

Possible mechanisms through which high meat intake may be related to ovarian cancer risk include the fact that the meat may contain carcinogenic heterocyclic amines (8, 48, 49) as well as the fat content of the meat (6). Fat is also a potential explanation for the opposite directions of the associations between poultry and red/processed meat and cancer risk as their fat content varies from $<4\%$ in lean poultry to $\approx 20\%$ in some types of red meat. Compared to red meat, poultry also contains a lower proportion of saturated fatty acids ($\approx 30\%$ compared with $\geq 45\%$) and a higher proportion of polyunsaturated fatty acids ($\geq 15\%$ compared with $<10\%$) (50). However, the relation between fat and ovarian cancer risk is unclear because, although meta-analyses (4, 51) of predominantly case-control data showed positive associations, a pooled analysis (6) of 12 cohort studies showed no association between total, monounsaturated, polyunsaturated, *trans*-unsaturated animal or vegetable fat intake and ovarian cancer risk and only a weak positive association for saturated fat intake. Furthermore, extra adjustment for fat in our analyses did not materially change the observed associations, which suggested that these were not due to the fat content of the foods.

Another possible mechanism whereby high processed meat intake could increase the risk of cancers is via the endogenous formation of nitroso compounds (4). Evidence regarding the effect of N-nitroso compounds on ovarian cancer risk is currently limited, although one Chinese case-control study (22) reported no association with the intake of salted animal foods that contain large amount of nitrites and nitrates. However, the authors (22) noted that the consumption of these foods is low in China, as they are relatively expensive.

In general, the data regarding the association with fish intake are inconsistent. The SWH and AOCS suggested an inverse association with the consumption of total fish and fatty fish, with weak or no effects seen for nonfatty fish and shellfish. In the meta-analysis, we observed a borderline significant inverse association with total fish intake, although the data were very heterogeneous. However, previous studies did not separate fatty and nonfatty fish; thus, it is possible that a weak overall association could mask a stronger inverse association with fatty fish. Further evidence supporting the hypothesis that fish consumption may reduce risk comes from a recent cohort study (52) that showed that, compared with meat eaters, vegetarians who also consumed fish had a somewhat lower risk of ovarian cancer (RR: 0.37; 95% CI: 0.18, 0.77) than vegetarians who did not eat fish (RR: 0.69; 95% CI: 0.45, 1.07). Overall, an inverse association between fish and ovarian cancer is biologically plausible because fish, in particular fatty fish, are a good source of omega-3 fatty acids, which may possess anticarcinogenic properties in relation to different type of cancers including ovarian cancer (9, 53). A meta-analysis (54) showed an inverse association between the intake of omega-3 polyunsaturated fatty acid and ovarian cancer.

As with any epidemiologic study, the SWH and AOCS data sets had a number of strengths and limitations. The major strengths are the combined numbers of participants, the use of population control subjects, and the high response rates for cases. A common reason for nonparticipation for a case was illness or death; thus, selection bias could have been introduced if any of the food items studied influenced survival. However, the results did not vary substantially when we stratified the SWH and AOCS data by stage of disease at diagnosis, a strong predictor of survival, which suggested that there was little selection bias from the nonparticipation of cases. A weakness was the lower response rate among control subjects, particularly in the AOCS (47%). Comparison of the AOCS control data to data from the Australian National Health Survey (55), a representative survey of the Australian adult population conducted in 2004 with a reported 90% response rate, showed similar distributions of education level, parity, body mass index, and smoking (ever/never) (56). Thus, it is unlikely that nonresponse resulted in an appreciably biased group. To minimize the possibility of recall bias, participants were asked about food consumption 1 y before the study or, for cases, 1 y before their diagnosis, and cases were recruited as soon as possible after diagnosis. If the presence of disease influenced the reporting of diet among cases, one might expect this effect to be greatest among those with more advanced cancer. However, the results did not vary appreciably by stage of disease. It is also possible that the observed associations were due to confounding by unmeasured characteristics. Adjustment for strong ovarian cancer risk factors such as age, parity, and oral contraceptive use had little effect on the effect estimates, and further adjustment for a range of other potential confounders did not appreciably alter the risk estimates. It seems unlikely that residual confounding because of some other unidentified risk factor could explain the findings.

The results of a meta-analysis can also be biased if studies that find an association are more likely to be published than those with null results or if the results of the individual studies that contribute to the meta-analysis are biased in some way. We showed no statistical evidence of publication bias; furthermore, many of the studies published their data for meat as part of a larger evaluation of diet. Thus, null and nonnull findings for meat would be reported equally. To guard against the latter possibility, we included only those studies that had adjusted for important confounders and also stratified our results by study type. In addition, we conducted extensive sensitivity analyses excluding studies that did not meet specific criteria for adjustment or study design; none of these exclusions appreciably altered any of our overall estimates, which suggests that these estimates are reliable.

In conclusion, our findings from 2 population-based case-control studies and a meta-analysis suggest that the high intake of processed meat may be associated with a higher risk of ovarian cancer, whereas high poultry or fish intake may be related to a lower risk of ovarian cancer. This suggests that by following common dietary guidelines to reduce the intake of processed meats and increase the intake of poultry and fish, women may also reduce their risk of ovarian cancer.

Full membership of the AOCS group is listed at http://www.aocstudy.org/; the Australian Cancer Study investigators are Adéle C Green, Peter G Parsons, Nicholas K Hayward, Penelope M Webb, and David C Whiteman.

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